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EXAMINER	
ANGELL, JON E	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 04/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/805,432	BUSCHMANN ET AL.	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,6,10-12 and 24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,6,10-12 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' paper filed 11/29/04 is acknowledged. The 11/29/04 paper indicated that Applicants have not received an Office Action in response to their communication filed 4/17/04. This communication is responsive to the response filed by Applicants on 5/17/04.

The amendment filed 5/17/2004 is acknowledged. The amendment has been entered. Claims 1, 3, 4, 6, 10-12 and 24 are currently pending in the application and are addressed herein.

Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

The response to Applicants' arguments is located after all rejections.

Drawings

The color drawings and the petition under 37 CFR 1.84 filed 6/4/2003 is acknowledged. The petition has been scanned, however, the color photographs have apparently been misplaced by the Office during the process of scanning the file. A search for the color photographs has been initiated, however a decision on the petition cannot be issued until the color photographs have been reviewed. As such, a decision on the petition will be issued once the color photographs have been located and reviewed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 4, 6, 10-12 and 24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection, (new grounds of rejection necessitated).** 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

MPEP §2163.06 notes:

If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).

MPEP §2163.02 teaches that:

Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application.

MPEP §2163.06 further notes:

When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure. (Emphasis added).

Claim 1 has been amended to add the following limitation (underlined): "administered intra-arterially". Applicants have indicated in the response filed 5/17/04 simply that "the claims are supported throughout the specification" and do not indicate the precise location where specific support for the amendment can be found. Although a thorough search of the specification was performed by the Examiner, no specific support for "administered intra-arterially" can be found.

Regarding the limitation "administered intra-arterially", page 6 of the specification discloses the following routes of administration: intravenous, intraperetoneal, subcutaneous, intramuscular, topical or intradermal (see last paragraph). Furthermore, working Example 3 also indicates that the route of administration is "locally, directly into the collateral circulation" (see page 20, last paragraph). It is noted that "locally, directly into the collateral circulation" is not considered support for the claimed method of delivery. First, the disclosure does not disclose "intra-arterially" delivering the protein. Furthermore, the limitation "administered intra-arterially" is not commensurate in scope with the disclosure in Example 3 because the instant claims are not limited to "locally, directly into the collateral circulation" but rather encompass intra-arterial delivery including and intra-arterial administration at a non-local site.

Therefore, the indicated limitation is considered new matter and the instant rejection is proper.

Applicants are asked to indicate the precise page and line number where specific support for the above-indicated limitation.

Claims 1, 3, 4, 6, 10-12 and 24 also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a written description rejection (new grounds of rejection).**

The instant claims are drawn to a method wherein transforming growth factor beta-1 (TGFβ1) is administered intra-arterially, wherein said TGFβ1 is a polypeptide. It is acknowledged that the claims have been amended to delete language specifically claiming derivatives and functionally equivalent substances, however, the recitation "wherein said TGFβ1 is a polypeptide" does not limit the instant claims to a specific TGFβ1 polypeptide because the claims encompass a TGFβ1 polypeptide (i.e., any TGFβ1 polypeptide). It is noted that the specification discloses,

> "In the context of this invention the term 'transforming growth factor beta 1' or 'TGFβ1' refers to proteins and peptides which act on macrophages and which are capable of promoting collateral artery growth by direct activation, proliferation and/or potentiation of the effector functions of resident and newly recited macrophages on blood vessels. The present invention also comprises substances which are functionally equivalent to TGFβ1 in that these substances are capable of electing the aforementioned biological responses. The action of the employed in the present invention may not be limited to the above-described specificity but they may also act on, for example eosinophils, lymphocyte subpopulations and/or stem cells." (See page 3, last paragraph)

> and

> "The TGFβ1 to be employed in the methods and uses of the present invention may be obtained from various sources described in the prior art; see, e.g., Klagsbrun, Annu. Rev. Physiol. 53 (1991), 217-239. The potential exists, in the use of recombinant DNA technology, for the preparation of various derivatives of TGFβ1 comprising a functional part thereof or proteins which are functionally equivalent to TGFβ1. In this context, as used throughout this specification "functional equivalent or "functional part" of TGFβ1 means a protein having part or all of the primary structural conformation of TGFβ1 possessing at least the biological property of promoting at least one macrophage or

> granulocyte effector function mentioned above. The functional part of said protein or the functionally equivalent protein may be a derivative by way of amino acid deletions, substitutions, insertions, additions and/or replacements of the amino acid sequence, for example by means of site directed mutagenesis of the underlying DNA...
> TGFβ1 or functional parts thereof or proteins which thereto, may be produced by known conventional recombinant techniques employing the amino acid and DNA sequences described in the prior art... For example, TGFβ1 may be produced by culturing a suitable cell or cell line which has been transformed with a DNA sequence encoding upon expression under the control of regulatory sequences TGFβ1 or a functional part thereof or a protein which is functionally equivalent to TGFβ1." (See p. 5)
>
> And
>
> "In this context, it is understood that TGFβ1 to be employed according to the present invention may be, e.g., modified by conventional methods known in the art. For example, it is possible to use fragments which retain the biological activity of TGFβ1 as described above, namely the capability of promoting collateral arterial growth." (See p. 10, last paragraph)

Therefore, the specification clearly contemplates using variants, derivatives, fragments, etc. of TGFβ1 in the instant invention. It is noted that the recitation "wherein said TGFβ1 is a polypeptide" in the claim only limits the TGFβ1 to **a polypeptide** (i.e., any TGFβ1 polypeptide including any of the variant, derivative, fragment TGFβ1 polypeptides contemplated in the specification). Therefore, in view of the disclosure of the specification (indicated above), the claims encompass any TGFβ1 polypeptide, including fragments, variants, derivatives, etc.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a TGFβ1 polypeptide (i.e., any TGFβ1 polypeptide). As such, the claims encompass a genus of TGFβ1 polypeptides that is indefinite in size, but which possibly encompasses hundreds of

thousands of different molecules considering every possibly variant, derivative and fragment contemplated by the specification. It is noted that the prior art recognizes a family of TGFβ polypeptides now named TGFβ1 (formerly TGFβ), TGFβ2, TGFβ3, TGFβ4 and TGFβ5 which are highly homologous proteins, but which despite the nomenclature is totally distinct from TGFα (e.g., see Klagsbrun, document AS3 cited by Applicants). Although the TGFβ family of proteins comprises highly homologous members, the claims clearly encompass fragments, variants and derivatives of TGFβ1 which are not disclosed in the specification. Furthermore, there is no particular guidance to indicate which fragments, derivatives and variants of TGFβ1 encompassed by the claims would have the proper activity required for the claimed method.

Accordingly, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states, "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required.

See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 4, 6, 10-12 and new claim 24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

> A method for enhancing arteriogenesis and/or the growth of collateral arteries from preexisting arteriole connections and/or the growth of other arteries from preexisting arteriole connections wherein said method comprises contacting an organ or tissue having preexisting arteriole connections with TGFβ1 polypeptide by administering said TGFβ1 polypeptide locally, directly into the collateral circulation of said organ or said tissue;

does not reasonably provide enablement for the full scope encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The original rejection was set forth in a previous Office Action. Below is a reiteration of the rejection as it applies to the instant claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The instant claims are drawn to a method for enhancing arteriogenesis and/or growth of collateral arteries and/or other arteries from preexisting arteriolar connections by contacting an organ or tissue having preexisting collateral arteriolar connections with TGFβ1 administered intra-arterially, wherein said TGFβ1 is a polypeptide. Therefore, the nature of the invention is enhancement of arteriogenesis/artery growth for therapeutic purposes by administration of a pharmaceutically active compound.

The breadth of the claims

The breadth of the claims is very broad. For instance the claims encompass administering any TGF-beta 1 polypeptide including variants, fragments, etc., wherein the TGFβ1 polypeptide is administered to the subject intra-arterially. It is noted that the instant claims are not limited to delivering the TGFβ1 polypeptide locally, directly into the collateral

circulation of the organ or tissue. In fact the claims encompass administering the TGFβ1intra-arterially to any artery in the subject, including an artery that is not local to the target tissue, including administration of the TGFβ1 intra-arterially to an artery in the leg with the expectation that the administration can specifically deliver the polypeptide to the target tissue. It is noted that the claims explicitly indicate that the target can be a "cerebral occlusive disease". Therefore the claims encompass an intra-arterial administration in a leg artery such that the administration results in enhanced arteriogenesis (etc.) in the brain of a subject having cerebral occlusive disease.

The unpredictability of the art and the state of the prior art

There are a number of problems recognized in the art with respect to administration of a protein pharmaceutical for treatment of disease, and specifically with the treatment to enhance arteriogenesis.

For instance, Shire in Biopharmaceutical Drug Design and Development (Wu-pong et al. Eds, Humana Press; Chapter 9; pages 205-238) teaches some of the problems associated with protein as pharmaceutical agents. Specifically, Shire teaches,

> "The formulation of protein therapeutics is more difficult than for traditional small-molecule drugs, because of the complex composition and physical properties of the proteins. In particular, the importance of maintaining protein confirmation makes this task especially difficult. Loss of protein activity or increased immunogenicity can result without any covalent chemical modifications. Many of the degradative pathways in proteins, such as proteolysis, deamidation, oxidation, or self-association, will be subject to a diverse set of solution conditions. Generally, especially for a liquid formulation, it is not possible to produce a formulation that will eliminate all of the potential routes of inactivation." See paragraph bridging pages 231-232.

Scholz et al. (Angiogenesis Vol. 4; p. 247-257; 2001) indicates the unpredictable nature of arteriogenesis as a therapeutic method for treating vascular diseases. Specifically, Scholz teaches,

"Collateral vessels exhibit the same morphology whether they had formed in the heart, limbs or brain or in dogs, rabbits or mouse. They are tortuous because they also increase lengthwise in a restricted space. In animals larger than the mouse, they develop an intima, and initially, many arterioles participate in arteriogenesis, but only a few mature into large arterial channels which, when arterial occlusion had proceeded slowly enough, can replace the occluded artery to a significant proportion. Therapy with a single growth factor in animals with occluded femoral arteries significantly increased the speed of arteriogenesis but does not significantly increase the level of adaptation. It appears that the master gene for arteriogenesis still awaits discovery." (See p. 247, abstract).

Therefore, it is unpredictable that a protein therapy could be effectively used to treat any vascular disease.

Working Examples and Guidance in the Specification

The specification indicates one example where TGF-beta polypeptide (0.48 ug/kg/day) was administered locally, directly into the collateral circulation of rabbits comprising a femoral artery ligation (see example 3, p. 20-23). It is disclosed, "TGF-beta 1 infusion for a time period of one week had significantly increased the number of visible collateral arteries as compared to the PBS-control group... The results of the experiments performed in accordance with the present invention indicate that TGF-beta 1 is capable of mediating arteriogenesis, and/or the growth of collateral arteries and/or other arteries from preexisting arteriole connections by activation of the monocyte/macrophage pathway" (see p. 22, second and third paragraphs).

There is no indication that administration of the TGF-beta 1 polypeptide by any means other than local direct delivery into the collateral circulation of the target organ/tissue can stimulate arteriogenesis and/or growth of collateral arteries and/or growth of other arteries from

said collateral arteries. Furthermore, there is no indication that the treatment could effectively treat any vascular disease such as cardiac infarct or stroke.

Quantity of Experimentation

Additional experimentation is required in order to overcome unpredictable nature of protein therapy in general and the unpredictable nature of therapeutic arteriogenesis recognized in the art and effectively use the claimed method to the full scope encompassed by the claims. For instance, experimentation would have to be done in order to effectively deliver a protein therapeutic agent by any means other than local directly into the collateral circulation of the target organ/tissue in order to avoid protein degradation pathways (and the hosts immune response). Furthermore, one would have to show that the administration could effectively stimulate enough arteriogenesis or collateral (or other) artery growth effective to treat any vascular disorder including cardiac infarct, stroke, etc.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering the high degree of unpredictability recognized in the art, the breadth of the claims, the limited of working examples and guidance in the specification; and the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed method is undue.

Art Rejections

It is noted that the instant claims are drawn to intra-arterial administration of a TGFβ1 polypeptide; however, as indicated above, the claims are not limited to direct local delivery into the collateral circulation. Furthermore, it is noted that the instant claims are only enabled for administration of TGFβ1 polypeptide locally, directly to the collateral circulation of the target organ or tissue, for the reasons indicated above. Although the instant claims do not explicitly recite administration locally, directly to the collateral circulation of the target organ or tissue, in the interest of compact prosecution the following rejection(s) are set forth with respect to the enabled subject matter of the instant claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 12 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by van Royen et al. (JACC, Feb., 2000).

Van Royen teaches that TGFβ polypeptide (encompassed by the claims) is a powerful promoter of arteriogenesis. Specifically, van Royen teaches that the right femoral artery was ligated in 24 rabbits and TGFβ was directly infused into the collateral circulation. Van Royen teaches that the TGFβ administration resulted in an increase in the number of visible collateral arteries and an increase in the conductance of the collateral circulation compared to controls (see

abstract). It is noted that the ligation of the femoral artery taught by the reference is considered to be a surgical treatment that damages or destroys arteries (meeting the limitations of claim 10), and the local direct delivery to the collateral circulation is considered to be a directly to the target tissue (meeting the limitation of claim 24).

It is noted that the reference is an abstract published in February 2000 which was presented by Applicants (and others) at a scientific meeting.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over van Royen et al. (JACC, Feb., 2000) in view of US Patent 5,482,851(Derynck et al., previously cited).

Van Royen teaches that TGFβ polypeptide (encompassed by the claims), is a powerful promoter of arteriogenesis. Specifically, van Royen teaches that the right femoral artery was ligated in 24 rabbits and TGFβ was directly infused into the collateral circulation. Van Royen teaches that the TGFβ administration resulted in an increase in the number of visible collateral arteries and an increase in the conductance of the collateral circulation compared to controls (see abstract).

Van Royen is silent with respect to whether the TGFβ used in the method is a recombinant TGFβ or a non-recombinant TGFβ.

Derynck teaches a recombinant human TGFβ including methods of making and purifying recombinant human TGFβ (e.g., see abstract and Examples).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by van Royen such that TGFβ used is a recombinant human TGFβ (as taught by Derynck), with a reasonable expectation of success.

The motivation to use recombinant human TGFβ is provided by Derynck, which teaches,

> "TGF-beta prepared by purification from biological materials present a risk of contamination by infectious agents such as HTLV-III or hepatitis viruses. Accordingly, it is an object of this invention to prepare TGF-beta from sources that do not present a risk of contamination."

Therefore, one of ordinary skill in the art would have been motivated to specifically use the recombinant human TGFβ taught by Derynck in order to avoid possibly contaminating the subjects with an infectious agent.

Claims 1, 4 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over van Royen et al. (JACC, Feb., 2000) in view of Asahara (Circulation, 1995, Vol 92 (9, Suppl.), previously cited).

Van Royen teaches that TGFβ polypeptide (encompassed by the claims), is a powerful promoter of arteriogenesis. Specifically, van Royen teaches that the right femoral artery was ligated in 24 rabbits and TGFβ was directly infused into the collateral circulation. Van Royen teaches that the TGFβ administration resulted in an increase in the number of visible collateral arteries and an increase in the conductance of the collateral circulation compared to controls (see abstract).

Van Royen does not teach that the organ or tissue is further contacted with a growth factor or cytokine.

However, the prior art recognized that growth factors and cytokines were well known neovacularizing agents. In fact, the prior art recognizes that combining angiogenic factors can have a synergistic effect on neovascularization. For instance, Asahara teaches a method for inducing neovascularization by administering a combination of two angiogenic molecules: b-FGF and VEGF to rabbits ten days after surgical induction of unilateral hind limb ischemia (e.g., see abstract). Asahara teaches that the combination treatment of b-FGF and VEGF has a synergistic effect on angiogenesis in vivo. Specifically, Asahara teaches,

> "Combined administration of VEGF and bFGF stimulates significantly greater and more rapid augmentation of collateral circulation, resulting in superior hemodynamic improvement compared with either VEGF or bFGF alone. This synergism of two angiogenic mitogens with different target cell specificities may have important implications for the treatment of severe arterial insufficiency in patients whose disease is not amenable to direct revascularization." (Emphasis added, e.g., see abstract, as well as results section).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by van Royen such that the method comprised administration of TGFβ with VEGF or b-FGF (or any other angiogenic growth factor

or cytokine for that matter) to a subject after surgical treatment that damages or destroys arteries in order to augment collateral circulation, with a reasonable expectation for success.

The motivation to modify the method is provided by Asahara, who indicates that combinations of known neovascularizing agents can have a synergistic effect (augment) on collateral circulation and may have important implications for the treatment of vascular diseases (such as sever arterial insufficiency). It is noted that van Royen indicates that an effect of TGFβ is increased collateral circulation.

Claims 1, 10 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over van Royen et al. (JACC, Feb., 2000) in view US Patent 6,121,246 (Isner, previously cited).

The instant claims are drawn to a method comprising administering TGF-beta-1 to a subject (claim 1), wherein said method is applied to a subject suffering from a vascular disease or a cardiac infarct or a stroke (claim 10), wherein said vascular disease is arteriosclerosis and/or a hyperlipidemic condition, **a coronary artery disease**, cerebral occlusive disease, peripheral occlusive disease, visceral occlusive disease, **renal artery disease**, mesenterial arterial insufficiency or an ophthalmic or retinal occlusion (claim 11). (Emphasis added).

Van Royen teaches that TGFβ polypeptide (encompassed by the claims) is a powerful promoter of arteriogenesis. Specifically, van Royen teaches that the right femoral artery was ligated in 24 rabbits and TGFβ was directly infused into the collateral circulation. Van Royen teaches that the TGFβ administration resulted in an increase in the number of visible collateral arteries and an increase in the conductance of the collateral circulation compared to controls (see abstract).

Van Royen does not specifically teach that the TGFβ is administered to a subject suffering from a vascular disease or a cardiac infarct or a stroke such as the renal artery disease such as renal ischemia.

Isner teaches a method of treating ischemia in a subject by administering a nucleic acid encoding TGFβ directly to the site of ischemia, wherein the ischemia can be cardiovascular ischemia and/or renal ischemia (e.g., see abstract or column 2, lines 54-61). Although Isner only teaches administration of a nucleic acid encoding TGFβ, it would have been prima facie obvious that the TGFβ polypeptide could be used to treat ischemia because one of ordinary skill in the art would recognize that a method comprising administering a nucleic acid encoding TGFβ must result in the expression of the TGFβ polypeptide in order for the treatment to be effective. That is, it would be readily recognized to an ordinary artisan that the functional element of the gene therapy method is the TGFβ polypeptide. Furthermore, there is an expectation of success that the TGFβ polypeptide administration could treat the ischemia based on the teachings of van Royen, indicated above.

It is noted that the cardiovascular diseases indicated in the instant claims, as well as cardiac infarct and stroke, all involve ischemia (generally recognized in the art as inadequate blood supply (circulation) to a local area).

Therefore, it would have been prima facie obvious to one of skill in the art at the time the method taught by van Royen could be used to treat ischemia (including renal ischemia, cerebral ischemia, as well as ischemia due to cardiac infarct, stroke, etc.) with a reasonable expectation of success, in view of the teachings of Isner.

One of ordinary skill would have recognized that TGFβ could be used to ameliorate the symptoms of ischemia based one the teachings of Isner and van Royen. Furthermore, one of ordinary skill in the art would have been motivated to use the TGFβ polypeptide based on the explicit teaching by van Royen that TGFβ is a powerful promoter of arteriogenesis and, "Arteriogenesis... is the only satisfactory adaptation to restore an efficient blood flow to ischemia territories."

Response to Arguments

Applicant's arguments filed 5/17/04 have been fully considered but they are not persuasive.

With respect to the enablement rejection, the Applicants argue that administration of protein was known in the art thus making the instant claims inherently enabled. Applicants also argue that Shire does not support the enablement rejection, because, Applicants contend, Shire does not assert that the instant method is not possible, but suggests that intra-arterial delivery of polypeptides was known in the art.

In response to Applicants arguments, it is acknowledged that methods involving intra-arterial delivery of therapeutic polypeptides were known in the art. However, this does not overcome the rejection. First, it is respectfully pointed out that the issue is not simply of whether or not the therapeutic protein can be delivered intra-arterially, but rather are the claims enabled for the full scope that they embrace. The instant claims have been amended such that the method now explicitly indicates that the TGFβ1 is delivered "intra-arterially", however there is no indication where, with respect to the target tissue/organ the intra-arterial delivery occurs. As such, the method still encompasses administering TGFβ1 polypeptide to an artery that is distal to

the target organ/tissue with the expectation that the delivery will have a specific effect (enhanced arteriogenesis, etc.) at a specific location in the subject's body. As indicated in a previous Office Action, Shire teaches,

> *"The formulation of protein therapeutics is more difficult than for traditional small-molecule drugs, because of the complex composition and physical properties of the proteins. In particular, the importance of maintaining protein confirmation makes this task especially difficult. Loss of protein activity or increased immunogenicity can result without any covalent chemical modifications. Many of the degradative pathways in proteins, such as proteolysis, deamidation, oxidation, or self-association, will be subject to a diverse set of solution conditions. Generally, especially for a liquid formulation, it is not possible to produce a formulation that will eliminate all of the potential routes of inactivation." See paragraph bridging pages 231-232.*

Therefore, Shire clearly indicates a number of obstacles that one of skill in the art would recognize as problems with respect to injecting a polypeptide into an artery and expecting the polypeptide to have a specific effect at a specific site that is not in the local area of the injection and to also expect that the polypeptide does not effect any non-specific site. For instance, using the instant method as an example, one of skill in the art would not expect that the TGFβ1 polypeptide could be injected into an artery in the foot of a human subject and expect that administration to result in enhanced arteriogenesis specifically in the subject's brain and nowhere else. There is no teaching in the prior art that such an administration of any therapeutic polypeptide could be so administered and result in such an effect. If Applicants are aware of any such prior art they are asked to submit it for the Examiner's consideration.

Furthermore, the working examples disclosed in the instant application indicate that the methods used to deliver the therapeutic polypeptide (TGFβ1) was delivered "locally, directly into the collateral circulation" (see p. 20, Example 3). There are no working examples indicating

that the polypeptide could be delivered distally by directly injecting the collateral arteries that are distal to the target tissue/organ.

It is noted that new claim 24 has been added further limiting claim 1 to "wherein the TGFβ1 is delivered directly to said organ or tissue". However, careful reading of the claim language reveals that the claim encompasses delivering the TGFβ1 polypeptide intra-arterially into any artery and then having the polypeptide delivered directly to the tissue or organ, there is no indication where the artery is with respect to the target tissue/organ. Therefore, the claim still encompasses intra-arterially delivering the polypeptide into an artery that is distal to the target tissue/organ. The problems indicated above are still applicable to this situation, thus the claim is not fully enabled.

With respect to the art rejections, Applicants have presented specific arguments to the art rejections based on Roberts (e.g., see pages 5-9 of the response filed 5/2004). Applicants' arguments are acknowledged and have been fully considered. With respect to the rejections, it is noted that the instant claims have been amended to limit the claims to intra-arterial administration of a TGFβ1 polypeptide. Roberts does not teach intra-arterial administration. Therefore, the rejection of the instant claims has been withdrawn. Applicant's additional arguments with respect to any other issues of the rejections based on Roberts are now moot as the rejection has been withdrawn for the reasons indicated.

With respect to the secondary references as they are applied in the instant rejections, Applicants arguments have been fully considered, but they are not persuasive.

With respect to the Ashara reference, Applicants argue that Ashara is drawn to enhancing angiogenesis and refers to their arguments with respect to the differences between angiogenesis and arteriogenesis (e.g., see p 7-8 of the response). It is acknowledged that there is an art recognized difference between angiogenesis and arteriogenesis, as indicated by Applicants. However, the effect of the combination treatment was an increase in collateral circulation, which is an effect also taught by van Royen. Therefore, it would have been obvious to one of ordinary skill in the art to combine TGFβ and VEGF or bFGF in a method to augment collateral circulation in order to treat a vascular insufficiency, based on the teachings in the cited prior art that TGFβ, as well as VEGF and bFGF treatments can augment collateral circulation regardless of VEGF and bFGF specific activity (i.e. regardless if they are angiogenic and/or arteriogenic factors) and the instant rejection is proper.

With respect to the Dernyck reference, Applicants do not specifically address the teachings of Dernyck. Applicants correctly point out that the rejection was indicated as a rejection of claims 1 and 2, when claim 2 was not pending (i.e., claim 2 was cancelled). It is noted that the rejected claims should have been claims 1 and 3. The inclusion of claim 2 and omission of claim 3 was a typographical error by the Examiner as claim 2 was indeed cancelled. The rejection should have been over claims 1 and 3 as claim 3 is drawn to the use of recombinant TGFβ. Absent any specific arguments against Dernyck, the instant rejection is proper.

With respect to the Isner reference, Applicants argue that Isner teaches a method for treating ischemic tissue in a mammal by injecting an effective amount nucleic acid, which is in contrast to the instant invention which is concerned with injection of protein (see p. 9). In response, it is noted that although Isner only teaches administration of a nucleic acid encoding

TGFβ, it would have been prima facie obvious that the TGFβ polypeptide could be used to treat ischemia because one of ordinary skill in the art would recognize that a method comprising administering a nucleic acid encoding TGFβ must result in the expression of the TGFβ polypeptide in order for the treatment to be effective. That is, it would be readily apparent to an ordinary artisan that the functional element of the gene therapy method is the TGFβ polypeptide. Furthermore, van Royen clearly indicates that TGFβ polypeptide can increase collateral circulation by promoting arteriogenesis which is "the only satisfactory adaptation to restore an efficient blood flow to ischemic territories. Therefore, the rejection involving Isner are proper.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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